REMARKS

Summary of Amendments

The specification and abstract are amended to refer to the amino acid sequences by SEQ ID NO:. Claim 1 is amended to avoid objection and rejection under 35 USC 112. Claims 6 and 7 are cancelled. Claim 14 is amended to avoid rejection under 35 USC 112.

Status of Claims

Claims 1 and 11-19 are pending. Claims 11-13 and 15-19 have been withdrawn from consideration by a restriction requirement which has been repeated but not stated as being made final. Claim 1 has been twice amended. Claims 11, 12, 14, 17 and 18 have been once amended.

The Restriction Requirement

Election was made in response to the initial restriction requirement dated September 4, 2002 without traverse. The further requirement made in the instant office action is traversed, and it is requested that it be reconsidered and withdrawn.

In response to the restriction requirement dated September 4, 2002, the peptide composition claims (Group I--claims 1, 6-7, and 12-14) were provisionally elected. In response to the further requirement to elect a single peptide, the peptide of SEQ. ID. No. 3 was designated. In response to the requirement to list the claims readable thereon, claims 1-2, 4-7 and 12-14 were itemized. As correctly pointed out by the Examiner in the outstanding office action, claims 2 and 4-5 were previously cancelled. The correct statement of claims readable on the designated peptide is 1, 6-7 and 12-14. By amendment above, claims 6-7 are cancelled. The elected claims remaining pending which read on the elected peptide are 1 and 12-14.

In the present office action, the examiner has asserted that claims 6-7 and 12-13 are drawn to a nonelected invention and refused examination. The assertion is traversed, but it partly made moot by the cancellation of claims 6-7.

Prior to the present amendment, claims 1 and 12-13 read as follows:

1. (Amended) A composition of matter comprising ADESH is a synthetic peptide consisting of SEQ ID NO: 3 mimics the biological properties of the whole NGF molecule derived from venom.

12. (Amended) A composition of matter comprising a peptide consisting of at least the first five amino acids from the N-terminal of SEQ ID NO: 2 and no more than 25 amino acids total.

13. A composition of matter as in claim 12 wherein the peptide contains no more than 15 amino acids total.

SEQ. ID. No. 3 is:

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Asn Leu Gly Glu His Pro Val Cys Asp Ser
                5                   10
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SEQ. ID. No. 2 is:

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Asn Leu Gly Glu His Pro Val Cys Asp Ser Thr Asp Thr Trp Val
                5                   10                  15
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The first 10 amino acids of Sequence I.D. No: 2 are constituted by Sequence I.D. No: 3. It follows that the first 5 amino acids of Sequence ID No.: 2 are identical to the first five amino acids of Sequence ID No.: 3.

The requirement (which was complied with) made in the application on July 3, 2002 to refer to sequences in the claims by "SEQ ID NO" obfuscates the relationship between these claims. Reproducing the claims by spelling out what applicant was required to incorporate by reference

much more concisely reveals the relationship between the claims as follows:

1. (Amended) A composition of matter comprising ADESH is a synthetic peptide consisting of

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Asn Leu Gly Glu His Pro Val Cys Asp Ser
                5                   10
```

mimics the biological properties of the whole NGF molecule derived from venom.

12. (Amended) A composition of matter comprising a peptide consisting of at least the first five amino acids from the N-terminal of

```
Asn Leu Gly Glu His Pro Val Cys Asp Ser Thr Asp Thr Trp Val
                5                   10                  15
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and no more than 25 amino acids total.

13. A composition of matter as in claim 12 wherein the peptide contains no more than 15 amino acids total.

Claims 12 and 13 are broader than claim 1 since the claim 1 peptide (a 10 amino acid peptide) described as a "synthetic peptide consisting of

```
Asn Leu Gly Glu His Pro Val Cys Asp Ser
                5                   10
```

mimics the biological properties of the whole NGF molecule derived from venom"

will always meet the limitations of claim 12 wherein the peptide is described as consisting "of at least the first five amino acids from the N-terminal of

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Asn Leu Gly Glu His Pro Val Cys Asp Ser Thr Asp Thr Trp Val
                5                   10                  15
```

and no more than 25 amino acids total" and always meet the limitations of claim 13 wherein the claim 12 peptide is further restricted to one which "contains no more than 15 amino acids total." That the claim 1 peptide is "synthetic" and mimics the biological properties of the whole NGF molecule derived from venom" makes claim 1 narrower, not broader, than claims 12 and 13. All of claims 1 and 12-13 therefore read on the elected species, which is SEQ. ID. No: 3 and these

claims should all have been acted on.. The assertion that unity of invention as between these claims is lacking is therefore in error, and the action taken of refusing to examine claims 12-13 is further in error. This is applicant's first opportunity to request reconsideration of this newly stated requirement, and fulfills a condition precedent to taking recourse by petition under 37 CFR 1.144. Reconsideration and withdrawal of the requirement as pertains to claims 12-13 is requested.

Objection to the specification for lacking sequence requirements

The specification has been objected to for failing to reference sequences by SEQ ID NO:. The objection is obviated by the above amendment which references the recited sequences by SEQ. ID. NO. The amendments are fully supported by the sequence listing and do not constitute new matter. Reconsideration is requested.

Claim objections

Claim 1 is objected to on the basis of grammatical insufficiencies. The objection is traversed but is obviated by the present amendment. Reconsideration is requested.

Claim rejections

Rejections under 35 USC 112, first paragraph, of claim 14

Claim 14 is rejected under 35 USC 112, first paragraph, on the basis that the claimed subject matter is not disclosed in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, (Section 8 of the Office Action) and further for nonenablement (Section 9 of the Office Action). These rejections are traversed, but are at least partially obviated by the above amendment to claim 14.

Claim 14 has been amended to recite that the peptide "contains from 5 to 15 amino acids from the N-terminal of the SEQ. ID NO: 2." The amendment is supported at several places in the specification and does not constitute new matter. As indicated in the office action on page 7, "a

description of a genus may be achieved by means of a recitation of a representative number of genus members falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus." It is submitted that claim 14 as amended is in compliance with these guidelines.

The rejection set forth in Section 8 of the Office Action states:

> "While the specification discloses binding affinities of particular antibodies with respect to various specimens as disclosed in Tables II and IV, pp. 11 and 13, the specification fails to disclose the particular sequences used to generate the antibodies of the Tables and further fails to disclose the peptides capable of generating a response which corresponds to the claims."

The same statement is repeated in Section 9 of the Office Action.

Claim 14 (Amended) reads as follows:

> 14. (Amended) A synthetic peptide containing from 5 to 15 amino acids from the N-terminal of the SEQ. ID NO: 2 which produces an antibody which has a binding affinity to nerve growth factors from human body fluids and human origin eukaryotic cells which is higher than a binding affinity exhibited by an antibody produced in immunological response to a nerve growth factor derived from venom.

The antibody referred to has binding affinity to NGF.

Table II is captioned:

Table II

Immunological Properties of AD-15, AD-10 and AD-5:
ELISA titer for Binding Affinity to Anti-AD-10, Anti-V-NGF
and Anti-H-NGF

Table II does not reveal an antibody binding to NGF and is not intended as supportive of claim

14.

Table IV is captioned:

Table IV

ELISA Binding Affinity of Anti-ADESH, Anti-Venom NGF and Anti-Human NGF to NGFs from Various Sources.

Table IV is directed towards antibodies binding to NGF and is supportive of claim 14.

In describing the procedure resulting in Table IV, the specification states at page 9, lines 1-3 :

> **"Enzyme-Linked Immunosorbent Assay (ELISA):** The binding affinity of Anti-ADESH made against ADESH consisting of ten amino acids (AD-10), to various specimens known to contain NGF, such as venoms, body fluids, saliva, serum, urine etc. was studied by ELISA."

In defining AD-10, the specification states at page 8, lines 4-5:

> "Synthetic ADESH (AD-10) was constructed using the above amino acids sequence from N-terminal for ten amino acids N L G E H P V C D S."

Anti-AD-10 is thus the antibody made against AD-10, which corresponds to SEQ ID NO: 3. Table IV contains binding data only for this species. However, the specification teaches the production of antibodies to other ADESH species at page 8, lines 20-26 as follows:

> Adult Balb/C mice were used for immunization. The mice were used in compliance with the US Public Health Service Policy on humane care and use of animals. First injection consisted of the mixture 100 μg of each version of ADESH in 0.1 ml mixed with equal volume of Freund's complete adjuvant/mouse. The subsequent injections consisted of the mixture 100μg of ADESH and equal volume of incomplete Freund's adjuvant/mouse. The mice were injected intramuscularly (IM) six times two weeks apart. At the end of the immunization the mice were bled through the ophthalmic

veins and serum was separated.

The versions of ADESH referred to are set forth at page 8, lines 4-8 as follows:

> **Synthesis of ADESH:**
> Synthetic ADESH (AD-10) was constructed using the above amino acids sequence from N-terminal for ten amino acids N L G E H P V C D S. Two more versions of synthetic ADESH, termed AD-15 and AD-5, consisting of 15 and 5 amino acids respectively, were constructed; The peptides had the sequence: N L G E H P V C D S T D T W V for AD-15 and N L G E H for AD-5.

The specification thus explicitly teaches that the peptides containing 5, 10 and 15 amino acids, corresponding to SEQ. ID. NO: 4, SEQ. ID. NO: 3, SEQ. ID. NO: 2 produce antibodies.

It is asserted in the Office Action on page 9 that

> "There is no description of any structural molecule which produces an antibody which has a binding affinity to NGFs from human body fluids and human origin eukaryotic cells which is higher than a binding affinity exhibited by an antibody produced in immunological response to an NGF derived from venom."

The statement is incorrect. Table IV shows that the binding affinity of the antibodies made against SEQ. ID. NO: 3 (Anti-ADESH) had the highest binding affinity to NGFs derived from human sources (Chang, NB cells 8100 each), lesser to monkey and mouse (Vero, SP/2), and least to rat (PC12) cell derived NGF (page 13, lines 11-12). Table IV shows that the binding affinity of anti-V-NGF to Chang and NB cells was 2700 each, which is less. The specification defines anti-V-NGF at page 4, lines 15-17 as follows:

> Antibodies made against the peptide of the invention have a higher binding affinity for NGF of human origin (termed H-NGF) than antibodies which were made against the 116 amino acid NGF derived from venom (V-NGF, the antibody being Anti-V-NGF).

The 116 amino acid NGF referred to is SEQ. ID. NO: 1.

A routineer could easily make additional peptides which produced antibodies having the recited property by using the teaching of the specification without undue experimentation, especially in view of the above amendment. The specification discloses the particular sequences used to generate the antibodies of the Tables and further discloses a peptide in the middle of the claimed possibilities capable of generating a response which corresponds to claim 14. Reconsideration and withdrawal of the 35 USC 112 rejections is therefore requested.

Rejection under 35 USC 112 of claim 1

Claim 1 has been rejected under 35 USC 112, second paragraph. The rejection has been obviated by the amendment of claim 1. Reconsideration and withdrawal of the rejection is requested.

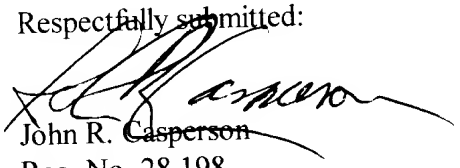
Further rejection of claim 14 under 35 USC 112

Claim 14 stands further rejected under 35 USC 112, second paragraph, because of the use of the term "NGFs", which apparently are not recognized in the literature in plural form. The claim has been amended to avoid use of the term. Reconsideration and withdrawal of this grounds of rejection is therefore also requested.

Conclusion

In view of the foregoing amendments and remarks, reconsideration and withdrawal of all grounds of rejection and objection and early notice of allowance is solicited.

Respectfully submitted:



John R. Casperson
Reg. No. 28,198

Please mail correspondence to:

John R. Casperson
PO Box 2174
Friendswood, Texas 77549

Tel. No. 281-482-2961

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN RESPONSE TO OFFICE ACTION DATED DECEMBER 26, 2002

In the specification

The paragraph beginning on page 4 line 7 and ending on page 4, line 10 is amended as follows:

The invention relates to a synthetic peptide consisting of at least the first five amino acids from the N-terminal of the sequence N L G E H P V C D S T D T W V (SEQ. ID NO: 2). The synthetic peptide mimics the biological properties of nerve growth factor (NGF) consisting of 116 amino acids.

The paragraph beginning on page 5 line 2 and ending on page 5, line 6 is amended as follows:

The inventive peptides can be generally described as compositions of matter consisting of at least the first five amino acids from the N-terminal of the sequence N L G E H P V C D S T D T W V (SEQ. ID NO: 2) and no more than 25 amino acids total. Usually, the inventive peptides will contain no more than 20 amino acids, and preferably no more than 15 amino acids. I have named the inventive peptides ADESH.

The paragraph beginning on page 6 line 1 and ending on page 6, line 12 is amended as follows:

The amino acid sequence of V-NGF derived from one species of cobra (Naja naja) venom is:

NH2-
Glu-Asp-His-Pro-Val-His-Asn-Leu-Gly-Glu-His-Pro-Val-Cys-Asx-
Ser-Thr-Ash-Thr-Trp_{20}-Val-Gly-Val-Lys-Thr-Thr-Ala-Thr-Asn-Ile-
Lys-Gly-Ala-Ser-Val-Ser-Val-Met-Glu-Asn_{40}-Val-Asn-Leu-Asp-Asn-
Lys-Val-Tyr-Lys-Gln-Tyr-Phe-Phe-Glu-Thr-Lys-Cys-Arg-Asx-Ser_{60}-
Asx-Pro-Pro-Glx-Pro-Gly-Cys-Lys-Gly-Ile-Asx-Thr-Glx-His-Trp-
Asx-Ser-Tyr-Cys-Thr_{80}-Thr-Ser-Asn-Ser-Phe-Ile-Lys-Ala-Leu-Thr-
Met-Asx-Glx-Gly-Gln-Ser-Ala-Trp-Arg-Phe_{100}-Ile-Arg-Ile-Gix-Thr-
Ala-Cys-Val-Cys-Val-Ile-Thr-Lys-Lys-Gly-Asn-
COOH

(SEQ. ID. NO: 1).

The paragraph beginning on page 7, line 22 and ending on page 8, line 2 is amended as follows:

The trypsin digested fragments in various concentrations were tested for neurite out growth on PC12 cells. Tissue culture plate having 24 wells were seeded with 10^5 PC12 cells in serum free Dulbeco Modified Eagle's medium (DMEM). The results were read after 72 hours for neurite outgrowth. The fraction showing the most neurite outgrowth at the lowest concentration was sequenced for its amino acids composition. Sequencing was contracted out to the Protein Core Laboratory of Baylor College of Medicine, Houston, Texas. The sequence for the fraction from the N-terminal was found to be: N L G E H P V C D S T D T W V (SEQ. ID. NO: 2).

The paragraph beginning on page 8, line 4 and ending on page 8, line 8 is amended as follows:

Synthetic ADESH (AD-10) was constructed using the above amino acids sequence from N-terminal for ten amino acids N L G E H P V C D S (SEQ. ID. NO: 3). Two more versions of synthetic ADESH, termed AD-15 and AD-5, consisting of 15 and 5 amino acids respectively, were constructed; The peptides had the sequence: N L G E H P V C D S T D T W V (SEQ. ID. NO: 2) for AD-15 and N L G E H (SEQ. ID. NO: 4) for AD-5.

In the abstract of the disclosure

The paragraph beginning on page 22, line 2 and ending on page 22, line 12 is amended as follows:

The purified nerve growth factor consisting of 116 amino acids from the venom of Naja kaouthia snake was fragmented by trypsin digestion. The fragments were isolated individually by high pressure liquid chromatography (HPLC). Thus separated fragments were tested for the biological activity of neurite growth on rat adrenal pheochromocytoma (PC12) cells. The fragment which showed the most activity was named ADESH. Subsequently, ADESH was sequenced. Synthetic ADESH was constructed using ten amino acids N L G E H P V C D S (SEQ. ID. NO: 3) of the fragment from its N-terminal is designated as AD-10. Different versions of synthetic ADESH such as AD-15 and AD-5 consisting of 15 and 5 amino acids respectively were constructed; having the sequence: N L G E H P V C D S T D T W V (SEQ. ID. NO: 2) for AD-15 and N L G E H (SEQ. ID. NO: 4) for AD-5. The synthetic AD-15 and AD-5 mimic the biological activity of the natural NGF.

In the claims

The claims have been amended as shown and discussed below.

Claim 1 is amended as follows:
1. (Twice Amended) A composition of matter [comprising ADESH is a synthetic peptide] consisting of a peptide as set forth in SEQ ID NO: 3 [mimics the biological properties of the whole NGF molecule derived from venom].

Claims 6-7 are cancelled.

Claim 14 is amended as follows:
14. (Amended) A synthetic peptide containing from 5 to 15 amino acids from the N-terminal of the SEQ. ID NO: 2 which produces an antibody which has a binding affinity to [NGFs] nerve growth factors from human body fluids and human origin eukaryotic cells which is higher than a binding affinity exhibited by an antibody produced in immunological response to [an NGF] a nerve growth factor derived from venom.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **Binie V. Lipps** **Frederick W. Lipps**	§	ATTY DCKT NO: FWLPAT013US
Serial No.: 09/613,355	§	Art Unit: 1647
Filed: July 11, 2000	§	Examiner: Turner, Sharon L.
For: **SYNTHETIC PEPTIDE FOR NEUROLOGICAL DISORDERS**	§	

Commissioner of Patents and Trademarks
Washington, DC 20231

TRANSMITTAL

Honorable Commissioner:

Transmitted herewith is:

(1) A Response to the Office Action dated December 26, 2002 concerning this application.

Respectfully submitted:

John R. Casperson
Reg. No. 28,198

Please mail correspondence to:

John R. Casperson
PO Box 2174
Friendswood, Texas 77549

Tel. No. 281-482-2961

I hereby certify that this correspondence and all documents referred to herein is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on

26 March 2003

3-26-03

by John R. Casperson, Reg. No. 28,198 (date)